



February 7, 2005

United States
Department of
Agriculture

CENTER FOR VETERINARY BIOLOGICS NOTICE NO. 05-05

Animal and Plant
Health Inspection
Service

Subject: Confidence Interval Estimation in Serological Interference Studies

Veterinary Services

To: Biologics Licensees, Permittees, and Applicants
Veterinary Services Management Team
Directors, Center for Veterinary Biologics

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Veterinary Services Memorandum (VSM) No. 800.203 includes several methods of demonstrating the absence of excessive interference in combination vaccines. Section IV.D. of the memorandum outlines the method of comparative serology, in which the Geometric Mean Titers (GMTs) of two vaccines are shown to be equivalent. This entails estimating a confidence interval for the GMT ratio. Recent discussions among members of the Animal Biologics Statisticians (ABS) group have produced suggestions for improving the precision of such estimates, so that the criteria of VSM No. 800.203 may be met with fewer animals. This notice describes an approach acceptable to the Center for Veterinary Biologics.

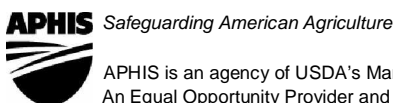
The width of the confidence interval is related to the variance of the response. In a properly designed and analyzed serological study, the variance of the response may be decomposed into its components, such as the variance of an animal's serum titer and the variance of the serological assay. A statistical model for estimating variance components can isolate and use the relevant components when estimating the confidence interval. In most situations, the resulting interval is narrower than one based on no decomposition of the variance components.

The objective of serological interference studies according to VSM No. 800.203 IV.D. is to draw conclusions about the immunogenicity of combination vaccines based on the average serological response of vaccinated animals. Such studies may benefit from reducing the impact of assay variance on interval estimates. Studies intended to do so should be designed to include multiple titrations on each serum specimen and analyzed appropriately.

The contents of this notice do not apply to any issue other than VSM No. 800.203 IV.D.

/s/ Richard E. Hill, Jr.

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Director
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